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Abstract

In this essay we examine whether a theoretical and conceptual framework for systems biology could be built from the Bailly-Longo (2008-9) proposal. These authors aim to understand life as a coherent critical structure, and propose to develop an extended physical approach of evolution, as a diffusion of biomass in a space of complexity. Their attempt leads to a simple mathematical reconstruction of Gould's assumption (1989) concerning the bacterial world as a "left wall of least complexity" that we will examine. Extended physical systems are characterized by their constructive properties. Time is acting and new properties emerge by their history that can open the list of their initial properties. This conceptual and theoretical framework is nothing more than a philosophical assumption, but as such it provides a new and exciting approach concerning the evolution of life, and the transition between physics and biology.

Keywords

Multilevel Modelling- System Biology- Critical states- Entropy- Conservative and Constructive Extensions- Complexity- Thought Experiment.

Introduction

Research concerning life necessarily deals with complexity. biological systems cannot obviously be reduced to very few components, like genes. The conception of the gene as a simple causal agent is based in the superposition of three assumptions: (1) a stretch of DNA determines which protein is made; (2) a stretch of DNA is the origin of an inheritable phenotype characteristic; (3) "once genetic information has passed into protein *it cannot get out again*" (Crick 1958). This notion is invalid because not all eukaryotic DNA codes for proteins, and DNA does nothing by itself. The egg machinery enables the DNA to be used to make proteins (Noble, 2008). Various molecular elements of living organisms (lipids, methyl and other epigenetic groups, etc.) are not coded for by DNA sequences. Thus, on one hand the gene is the causal agent, but on the other one it is the cell, or the tissue (Atlan 1997, 1999).

as mentioned by Von Westerhoff et al (2009) simple paradigms at work in classical physics (like the principle of minimum potential energy in mechanics, or in quantum mechanics) are

of no use in theoretical biology. Living organisms are open thermodynamical systems that function at a non-equilibrium steady-sate (Nicolis, Prigogine, 1989). To maintain this state, they need a metabolic activity that requires 14 proteins that cannot be disentangled from the activity of more than three hundred gene products. This number is too large for a simple bottom-up explanation (Von Westerhoff et al). Thus, new strategies are being proposed to explain biological phenomena. One of them proposes to generate hypotheses at a top-down level (as an example: Barabasi, 1999; Jeong-Barabasi, 2001) and replace them by more precise forms of the hypotheses "in a bottom-up" fashion (Von Westerhoff et al) before testing them. Another one proposes to *simultaneously* introduce assumptions at different levels of biological organization (Noble 2002, 2006 pp71-73, Soto 2004, and Lesne 2006).The "virtual heart", a computer reconstruction of the heart developed by Noble involves three levels: electrical excitation, blood vessels and muscle fibres (Noble 2002, p 76). These multilevel approaches deeply change the structure of scientific explanation. In contradiction with the so-called Occam's razor requirement[1]. rather than characterizing a system in terms of its physical constraints, physical and biological parameters are often coupled.

Could it be possible to find ***a conceptual and a theoretical framework*** to systemic approaches that will avoid statements such as: "science is either physics or stamp collecting" (Rutherford, quoted by Von Westerhoff et al, 2009)? We will not attempt to answer this question.. We will focus, instead, on the example of evolution, a process described by Gould (1996) as not completely governed by natural selection. According to him, neutral and random mutations occur at the lowest level (Kimura, 1968). At the highest level, massive extinctions are not due to adaptative struggles between individuals and/or species (Raup, 1984). Instead, massive extinctions result from accidental and catastrophic changes in environmental conditions. In contrast, the salient feature of life involves the stability of its bacterial mode, "physically constrained" from the starting point due to the chemistry of life and self-organization. Gould calls this symmetry breaking between simple physics and biology "the left wall of complexity" (1996). Gould's view emphasizes the tree of life with its maximum number of branches, and not the tiny right tail in the curve of evolution through a space of complexity. In other words, humans are just an accident and the bacterium the rule.

This paper will examine whether this description of evolution as the diffusion of biomass through a space of complexity ***could be fully explained by theoretical science*** by means of a new hypothesis positing that biological properties are nothing but extended physical ones, in the logical sense of the term (Bailly-Longo 2008, 2009). This explanation is highly incompatible with the characterization of the natural world as essentially determined at the physical level. This view of evolution is founded on the use of a new observable: "anti-entropy", that constitutes an extension to classical statistical mechanics, where scales can be decoupled, and where "positive" and "negative" entropy are defined by the use of simple distributions of probabilities. Anti-entropy is analysed in a perspective partially inspired from the "principle of order by order" proposed by Schrödinger, and in connection with a new diffusion equation of biomass through a "space of complexity" that is neither a normal physical phase space, nor the abstract Hilbert's space of quantum mechanics (2009). This explanation leads to a simple mathematical reconstruction of Gould's complexity curve of biomass (1989). This view of evolution remains speculative; however, philosophy doesn't have to deal only with empirical statements or nomological propositions. In spite of the fact that "the space of complexity" is yet to be verified, it provides a new and exciting approach

[1] Hypotheses should not be multiplied beyond necessity (Entia non sunt multiplicanda praeter necessitatem).

for a philosopher. Philosophy is not science, even if there is no scientific assumption that can be said to be philosophically free.

1- A problem coming from "What is life"?

As a starting point, we will use Schrödinger's informal and clever remarks as presented in his short text: *What is life?* (1944). On the one hand, he rejects the division between physics and biology and of a multilayered approach in natural sciences but, on the other, he strongly criticizes what he calls the "naïve approach of the physicist". Life is nothing alien to physics: "we must therefore not be discouraged by the difficulty of interpreting it by the ordinary laws of physics" (1944). However, life requires special attention.

First of all, statistic laws of physics and physical chemistry are inaccurate "within a probable relative error of the order of $1/\sqrt{n}$", if (n) is the number of molecules or of elements covered by the law. Thus, these laws apply only to very large populations of elements. After considering mitosis and meiosis mechanisms and crossing-over laws, Schrödinger assumes that the gene is nothing but a large molecule consisting of a rather short number of atoms. Delbrück's model concerning gene stability and mutations was not in contradiction with such an assumption. The final conclusion was that genes and gene actions are outside of ordinary statistic laws of physics, if not of quantum mechanics.

The Austrian physicist predicted that the remarkable stability of both genes and genetic recombination mechanisms require a specific chemical structure, i.e., an "aperiodic" one-dimensional crystal that conforms to the Heitler-London's forces. This was not a simple assertion founded on Delbruck's speculations; it must be understood as a physical assumption based on a theoretical distinction between the physics of gases and the chemistry of crystals. In a way, for Schrödinger, life is just a "clock work", but with a "very big grain of salt" (1944). Indeed, a clock-work is not a simple mechanical phenomenon. He argued that the regular pace of the clock must be secured by a comparatively weak spring, "that overcomes the small disturbances by heat motion" (1944). Thus, the clock's motion actually obeys a non-linear dynamic and differential equation. However, a living system is not a mere clockwork. Something must be added in order to make it alive, to work and to function. The chromosomal crystal, if it exists, must contain in its aperiodic structure a "code script" that "under suitable conditions" controls the development of the organism "into a black cock or a speckled hen", as an "architect's plan and a builder's craft in one" (1944, p23).

It should be noted that Schrödinger didn't simply assume that a biological function was present in a physical structure, as Mayr, Jacob or Monod did. Instead, he tried to provide the physical conditions that could explain its emergence. This approach led him to develop a special principle. Schrödinger argued that life cannot be explained by the mere use of negative entropy: "to put it briefly, we witness the event that existing order displays the power of maintaining itself and of producing orderly events" (1944, p 82). Thus, the biological organization is not only maintained by "extracting order" from the environment, as a simple open thermodynamic system far from equilibrium. Organization and evolution are coming from nothing but "a stream of order" "governing atoms". This stream of order is not merely what Prigogine called later a "dissipative structure" (1979, 1989). Schrödinger did not have the conceptual equipment to formulate more explicitly this strange assumption. Let's simply draw a double conclusion. In Schrödinger's views the "principle of order by order" is a

dynamical one. Life is not an association of atoms. Additionally, this "stream of order" is not fully explained by the natural selection principle.

2- Life as the diffusion of the biomass

Before examining what life is from Bailly-Longo's standpoint, we will introduce a preliminary remark. Current views on the origins of life assume that life had one or many historical origins, and it evolved from pre-existing non living physical systems. Thus, this view led to a research program to find the chemical and physical conditions that could explain the emergence of life. One way to address this question is to investigate how life started with prebiotic elements, passed to the step of functional molecules and finally how these functional molecules cooperated in a self-organized system of molecules (Kauffman 2000, Morange 2004). Instead, Bailly and Longo define the biomass (M) as a whole already present in the isolated bacterium, without any consideration to the initial chemical formation of the complexity (K) which characterizes (M). The symbol (M), characterizes alls reproductive, generative and plastic properties specifying that living matter is more than inert matter. Thus Bailly and Longo's explanation for the diffusion of the biomass requires ($K \geq 0$) in a certain way, a systemic approach that cannot be reduced to an initial bottom-up strategy, since they are no exploring causes. This scheme seeks new theoretical principles.

Following Bailly-Longo, and in accordance with Schrödinger's views, complexity is not simply investigated as "negative entropy" (basically nutrients) extracted from the environment by an open thermodynamic structure. Complexity (K), as linked to "*anti-entropy*" (S^-) is correlated with the formation of "multilevel, integrated and regulated organization" (2009)[2]. One could argue that negative entropy can always be reversed into a positive one. Yet, like in the relationship between matter and anti-matter (as a purely conceptual analogy), the addition of entropy and anti-entropy is not equal to zero. This addition produces a singularity that they call "an extended critical state," which is not outside the classical laws of thermodynamics, but which emerges from physically defined conditions. It would notably explain the tree of life with its maximum of branches as a gradual explosion of discontinuities. The *constitution* of the biomass results as a local decrease of disorder, in "an irreversible increase of global entropy" during a certain period of time. It is analogous to Schrödinger's first principle of "an order coming from disorder." However, the *diffusion* of biomass requires an additional explanation[3].

Fick's classical diffusion equation expresses how the concentration of a substance at any given point increases or decreases at a time rate ($\partial p/\partial t$) proportional to the surplus of concentration in the infinitesimal environment of this point[4]. This dissipative equation expresses an irreversible change in nature.

$$(1)\ \partial \mathrm{p}/\partial \mathrm{t} = D\nabla^2 \mathrm{p}$$

Along these same lines, Bailly and Longo's equation develops an idea that implies a «left wall of least complexity» (Gould, 1996). The formation of the first bacterium (whatever its origin) breaks a symmetry (the flat absence of life) by the constitution of the first organism, whose anti-entropy

[2] One could find very similar ideas in Kauffman (Investigations, 2000), or Simondon (1964).
[3] Of course, such a diffusion process has nothing to do with a molecular one. The biomass diffused is a macroscopic observable, and it diffuses along this new observable, anti-entropy.
[4] This equation is given as example in: What is life? (1944).

or complexity is > 0. The resulting random evolution “takes place toward the right" in a direction of increasing complexity, through which the biomass propagates (Bailly and Longo, 2009). Their explanation of this fact is based on the simple and general principle that diffusion preserves the original symmetry breaking, in this case the one at the origin of bacterial complexity. It gives a theoretical basis to Gould’s qualitative assertion founded on empirical observations.

Bailly and Longo examine how the biomass (M) diffuses ($\partial m/\partial t$) in a space of complexity (K) that replaces the simple physical phase space with state variables and state equations. This new space is characterized by three parameters: combinatorial, morphological and functional complexity that define anti-entropy as “organization,” a new observable proper to life. This diffusion expresses a random increase of complexity during time. It can be formulated by means of a balance equation that determines how, from an initial symmetry breaking present in the left wall, the biomass (M) is spent or diffused during evolution[5]. The equation ($D\partial^2 m/\partial K^2$) is the analogous to ($D\nabla^2$ p) in equation (1) so that[6]:

(2) $\partial m/\partial t = D\partial^2 m/\partial K^2 + am\ (t, K)$.

Finally, a linear solution of this differential equation can be found so that complexity (K) would keep on increasing over time, translating the irreversibility of this diffusion process in the space of complexity[7]. These authors predict that this “phylogenetic drift” is not a simple diffusion process exclusively involving random mutations, as in the neutral theory of molecular evolution proposed by Kimura (1968). This process also depends on the initial potential of complexity [am (t, K)] and not directly on the way by which inherited genetic variations could be selected. It should also be noted that complexity is not defined by simple allelic diversity, or by simple epistatic interactions between genes. These two points represent significant differences with Schrödinger’s, Crick’s, Mayr’s, and Monod’s positions. In conformity with Gould’s empirical assertions, complexity is a biological and organizational property that is not characterized solely at the level of genes, and by a presumed “genetic program”.

3- Would extended physical properties remain as simple conservative ones?

Bailly and Longo speak of extended physical properties in the “logical sense of the term”. This point deserves special attention, because in classical logic there are two very different characterizations of extension.

First, we will refer to the Löwenheim-Skolem’s theorem (LS), which is very often quoted and mentioned by philosophers of science (Van Fraassen, 2004) and philosophers of language (Quine, 1969). According to the LS theorem, ***a first order theory (T) that has an elementary extension (T*), also has an elementary substructure.*** A first order theory that we will symbolize (T) is a logical system that quantifies on simple variables (x, y, z), and not on

[5] The total biomass M (t) at time (t) will be the integral in dK, of m(t,K), with (m) for the density of the biomass. D is the “diffusion coefficient”. (K) is the complexity associated to anti-entropy.

[6] Bailly and Longo derive this equation from Schrödinger *operatorial approach* to energy expression at the origin of Schrödinger’s famous equation in quantum mechanics (a “diffusion” in an Hilbert space, over complex numbers). This technically justifies the linear dependence on the bio-mass (the am(t,K) component) and philosophically explains their understanding of “time as an operator”.

[7] $K(t \rightarrow \infty) \sim 2t\sqrt{}\ (aD)$.

functions (f, g, h). An extension concerns simply the "non categoricity" of the theory: (T) admits a class of interpretations or models (S) that have a greater cardinality than (T), and in which all axioms and formulas of (T) remain true. In other words, according to the upward version of the LS theorem mentioned here, a first order theory (T) is not able to control the cardinality of its models. This property does not mean that this extension is not a conservative one. There is no need to add an axiom or a formula in (T) in order to show that there are some models of (T) that do not have the same cardinality as (T). This would not be the case when examining Gödel's incompleteness theorems, or when dealing with a theory that we will symbolize (Th), since it admits the axiom of infinity. According to the first Gödel's proof, a formula G in a theory (Th) can be constructed by a recursive procedure, so that G can only be proved in an extension (Th*) and *not* in (Th). G can be constructed in (Th) without being proved in (Th). G is nothing but a constructive statement so that the list of axioms and formulae characterizing (Th) ***cannot be closed in (Th).*** This list is not a complete one.

Second, why do Bailly and Longo appeal to logic in the construction of a theoretical biological structure? In our opinion, it is both a philosophical and a speculative one, because it deals with a mere analogy and a metaphysical claim. In our view, science deals with symmetries and not with analogies. The French philosopher Simondon (1995) stated that analogy is identity between relations, and not "a relation of identity". Analogies can be formulated, but they cannot be formalized. Bailly-Longo's analogy concerns the relation between conservative and constructive extension in natural ***and*** in formal sciences. It is based on a metaphysical claim: logical and mathematical theories are human constructions ***in*** the natural world. It is not the natural world that would be the result of a human construction. Thus what happens in a theory can be related to what happens in the natural world. However, this relation is a metaphysical one. It cannot be reduced to a scientific explanation; it remains as pure speculation.

Next, we will explore the consequences of the Bailly and Longo proposal regarding a philosophy of evolution. They view evolution as a diffusion equation in a space of complexity, in which time *operates* a transformation More precisely, what does it take for symmetry breaking to occur, and when would time become .an operator, and not a simple variable- the exact opposite of Quantum mechanics. The addition of complexity as anti-entropy, a proper biological "observable" in the Bailly-Longo's diffusion equation, is ***the extension*** of thermodynamics as a physical theory. Yet, would it be a ***conservative extension,*** so that a new set of biological properties emerge or supervene in B (for "Biological level"), but depend on the same complete and causally closed physical basis P (for "Physical level")? Or would it be ***a constructive extension***? In other words, would (B) properties emerge in a natural system, and thus open the initial list of its (P) properties? The answer is unclear; because what is called "anti-entropy" is not simple negative entropy. Mathematically, it can be compared to the extension of Peano Arithmetic (PA) by a new symbol for infinity and an axiom ("there exist an infinite set") to obtain Zermelo-Frankel set theory (ZF). Physically, we have already compared it to the extension by the notion of anti-matter. However, this is just a comparison and it doesn't mean that anti-entropy is a simple physical property, like anti-matter!

Nevertheless, such an extension is realized by the production of a certain sort of singularity ***that is self-activating*** for a long period of time. "Anti-entropy" exists only in "an extended critical state," which is not a simple "critical point," but is instead a critical "long-lasting" transition which is not pointwise as in the physical theories of criticality (where

renormalization requires pointwise transitions[8]). That is, this state changes itself into a critical zone with respect to all the control parameters and it has a critical complex spatiality and dimension[9]. Such an extended critical state would not be a mere dissipative self-organized structure, like a flame, or a crystal. It would be some kind of "enlarged and complexified criticality". On the one hand, this state is just a critical dissipative structure, but on the other, it is also a self-activating structure. This paradoxical formulation ("self-activating one") involves the emergence in physics of a more complex type of self-organization. This system would be a self-referential one that is not entirely characterized by its first description, since it is acting on itself. Yet, the self is not a substance, but a simple constructive property. This property describes the relation between the initial description of a system (before) and its functioning (after). What the system was before is not what it is after. There is a strong form of irreversibility coming from the use of this epistemic operator, that we call a "chronological constraint". In our view, in Bailly and Longo's paper, this chronological constraint explains the use of time as an operator rather than as a variable. Coming back to Gould (1989), such a constraint would also explain the role of "history" in evolution, as a contingent process that can neither be characterized by chance, nor by determinism. History is a story that can only be retrospectively told and cannot be predicted. A natural system "at work" characterized by such a chronological constraint would be a structurally incomplete one, since the list of its properties would be the result of its construction.

What might be the physico-chemical conditions that would generate and sustain an extended critical activity? The cell is a closed physical space within a membrane however, the cell is also an open system far from equilibrium by virtue of its metabolic activity. The coupling of these two properties could explain that a critical state may exist beyond a mathematically instantaneous time. Simple critical systems are topologically and chronologically limited *at one point* by both distinctions between before/after, and inside/outside. The cell membrane is an *additional* condition that can explain how a physical structure can preserve and extend its criticality and the emergence of autonomy that is not simply self-organization. Through autonomy a system becomes an autopoïetic structure [F. Varela, (1979); Luigi Luisi (2003)] whereby the destruction and modification of all elements that it generates preserve its internal organization. ML Cardenas and E Cornish generated an experimental model for such a metabolism-replacement system (2002, 2007). This biological device is maintained, prolonged and differentiated for an *indefinite period of time,* if autonomy and self-organization are also *coupled* with replication (Maynard Smith; Morange, 2004). Replication has been partially modelled on cross-catalysis of proteins and oligonucleotides (G. Von Kiedrowski, 1994). It can emerge from specific biochemical conditions that are not those initially characterized by M. Eigen and P. Schuster (1979). Thus, *biological information is more than individuation*. Regarding Bailly and Longo's assumption, biological information is the fact that individuation is *continually transformed*, due to replication and inheritance, through extended critical transitions.

Biological information is also not genetic inheritance (Atlan, 1997, 1999). We will give three compelling examples that fit perfectly with this last assertion. The first one has an evolutionary meaning. It is the SOS black box in E. coli and Salmonella, discovered by M.

[8] In mathematics, the qualifier **pointwise** is used to indicate that a certain property is defined by considering each value $f(x)$ of some function f.

[9] They renew, in this way, an old philosophical idea already expressed by the french philosopher G. Simondon : « … l'individuation vitale ne vient pas après l'individuation physico-chimique, mais pendant cette individuation, avant son achèvement (…) en la rendant capable de s'étendre et de se propager avant l'itération de la structure parfaite capable seulement de se répéter » (1964, p 150).

Radman (1999a)[10]. In response to a stress signal coming from outside (induced by X rays), the Reca protein becomes a co-protease that cleaves the Lex repressor controlling the SOS black box. Mutator genes are activated. Polymerase proteins (IV and V) are synthesized. They repair the bacterial chromosome, inserting targeted and non-targeted mutations. Radman (1999a) called this a genome's reprogramming. Mutations are not simple stochastic events; they occur at specific moments and are amplified or repressed by this regulatory mechanism. Mutations don't have their origin in genes, or in stochastic events: a*n experimental multilevel approach* (molecular, organismic and populational) is necessary in order to characterize their occurrence. One could add an ecologic level, since Reca protein is also activating the Lambda phage (Sauer, 1982).

The second example concerns the regulatory functions due to epigenetic modifications of DNA and/or its packing into chromatin. It is well known that chromatin organization varies in space along the chromosome (heterochromatin vs. euchromatin), and in time along the cell cycle. Epigenetic modifications are implicated in this regulation process; histone deacetylases or methyltransferases are recruited and lead to the modification of the chromatin structure. In this regard, A. Lesne and J.M. Victor (2006) have shown that chromatin, as a "hyper-structure" characterized by physical parameters like robustness, elasticity and by topologic invariants, also has a complex role on the gene expression pattern. Its role is "both regulated and regulatory" (2006) by the fiber architecture of chromatin. For instance, mechanical constraints prevent the binding of transcription factors, when the DNA is strongly anchored on a nucleosome. However, when the histone tails are free due to the modification of electric charges, a first-occurring "intercalation" might induce allosteric conformational changes in the DNA ("buckling") that lower the energy barrier for further intercalations of proteins. These authors provide a *multi-level modelling* of this dynamical structure changing in space and in time.

The third one involves carcinogenesis. The "tissue organization field theory" (Soto and Sonnenschein, 2004) predicts that cancer cannot be explained by genetic mutations modifying the expression of genes in cells. Like aging, cancer is due to an alteration of tissues implying *simultaneously* local modifications and systemic properties, like the relation between support tissue (i.e., stroma, connective tissue) and parenchyma (i.e, the distinctive tissue of an organ, for example, an epithelium), or between cells and their extra-cellular matrix. Maffini et al (2004) have shown that the stroma – *and not the epithelium*- is a crucial target for carcinogens, a result that contradicts the so-called somatic mutation theory.

Conclusion

Bailly and Longo propose a speculative equation in order to partially explain the diffusion of bio-mass as a trajectory in a space of complexity and they suggest that this linear differential equation has a solution. Even if the so-called "space of complexity" is today nothing more than a theoretical possibility that must be better characterized, the philosophical key point for us is that they interpret this mathematical space in which anti-entropy is realized in biological criticality as an *extension* of the classical physical theoretical frameworks.

This biological space is mathematically and logically compatible with the simple physical one, but it cannot be reduced to it: in logical terms, it is a proper extension of it. Concerning anti-entropy *and* extended criticality, it is far from being proven that these extensions are conservative ones. The statements concerning classical physical properties are always true in

[10] See also Fox Keller's comments (2000).

such a complex space, but biological properties do not have a meaning in a simple physical space defined by physical or chemical state variables. Bailly and Longo's theory could also explain why simple physical observables (like elasticity, Lesne 2006) play a biological role that doesn't have a meaning in a simple physical system.

This approach is based on a mere ***philosophical*** analogy through which open formal systems can be compared with physical ones. This analogy cannot be scientifically tested or measured per se, and it doesn't have to be ***deduced,*** even though it might open a new field of scientific investigation. It is nothing but a metaphysical claim, which states, to put it simply, that we observe the world from inside, and that we cannot jump outside, by means of a formal and mathematical representation. In fact, there is no such cosmic exile. According to this approach, formal systems are nothing but natural events that can be compared with physical and biological events *inside* our world. And this world is not closed, like a *limited* object represented by a Super Laplacian eye. There is no metaphysical Laplacian eye in this physical world that is an open and *finite* one, not only for us, but in itself.

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